Archives of Disease in Childhood 1996;75:F38–F41

Natural history of trisomy 18

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Abstract

It has been suggested that survival in babies with trisomy 18 may be better than previously recognised, and that cardiac surgery may be justified. A population based study spanning seven years in one English health region is presented. The fetal prevalence at 18 weeks was 1 in 4274 and birth prevalence 1 in 8333 live births. Trisomy 18 was detected antenatally in 43% of cases, but almost 90% of those born without a diagnosis were known to be growth retarded in utero. More than 50% of liveborn infants were delivered by caesarean section. The median survival of those born alive was 3 days with no babies living longer than one year. Cardiac malformations were not universal but were present in more than 87% of those for whom there were data. However, in only three cases were cardiac problems implicated in the death of the infants.

Cardiac surgery is not likely to improve the survival of infants with trisomy 18 and at present cannot be justified. The most common mode of death was central apnoea.

(*Arch Dis Child* 1996;75:F38–F41)

Keywords: trisomy 18, prevalence, survival, cardiac surgery.

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Accepted 2 April 1996

Trisomy 18 is the second most common autosomal trisomy and has a quoted incidence of between 1 in 3000 and 1 in 8000.[1–3] Congenital heart disease is known to be commonly associated [2 4 5] and is frequently blamed by clinicians for the rapid death of babies with this condition. Despite the prolific descriptions published about trisomy 18, there is little population based information about mode of death and survival.[6] Clinical management of affected pregnancies and liveborn babies depends on accurate information about survival to enable parents, obstetricians, and paediatricians to plan future actions.[7 8] Such information can only be obtained by a prospective cohort study or from retrospective studies which encompass a defined population [2] so that ascertainment bias is minimised. We report a population based retrospective study of trisomy 18 in one English health region.

Methods

The Northern Health Region of England (now the Northern sector of the Northern and Yorkshire Health Region) is suited to population based studies as it has well defined borders and little cross referral. All fetal abnormalities are notified to the Northern Regional Fetal Abnormality Survey and perinatal and infant deaths to the Perinatal Mortality Survey. These surveys have been validated before [9] and were the source of all cases for the years between 1986-92. Each case was cross referenced with the three regional genetics laboratories to obtain accurate cytogenetic data with the regional paediatric cardiology database, to ascertain any congenital heart malformations. Antenatal data were obtained by examining the medical records of the affected women, and the medical and nursing notes of babies born alive provided demographic data, birthweight, history, and information about the mode of death.

The mode of death of the liveborn babies was categorised as following:

1 Never stabilised—died within the first 18 hours when management was withdrawn on clinical grounds.
2 Apnoea.
3 Sepsis.
4 Episodic cyanosis—cyanosis with insufficient evidence to ascribe it to apnoea.
5 Extubated— babies who died at more than 18 hours of age after withdrawal of support following a firm diagnosis of trisomy 18.

The number of births in the region for the seven year period was obtained from the Regional Perinatal Mortality Survey and the Office of Population Censuses and Surveys (OPCS).

Results

PREVALENCE

There were 66 fetuses (mean maternal age 30.9 years) with trisomy 18 at 18 weeks of gestation during 1986-92 and 282 583 births over the same period. Of the 66 affected pregnancies, 23 were terminated, six aborted spontaneously, three babies were stillborn and 34 were born alive. Thirty one male and 35 female fetuses were affected, but of 34 live babies, 23 were female and 11 were male. The observed fetal prevalence of trisomy 18 at 18 weeks of gestation was 0.234 per 1000 live births (1 in 4274) and the birth prevalence was 0.12 per 1000 (1 in 8333) live births.

ANTENATAL DIAGNOSIS

Trisomy 18 (or a major abnormality)was diagnosed antenatally in 28 cases. Of these, 23 pregnancies were terminated, three spontaneously aborted, and two were carried to term. Initial diagnosis was made by amniocentesis (n=14), ultrasound (n=13), or chorionic villus biopsy (n=1).[1] Amniocentesis or chorionic villus biopsy were performed on the basis of maternal age (mean age 40 years) in all but one case where amniocentesis was performed at 34

Table 1 Ultrasound findings in non-liveborn fetuses

Abnormality	*No of cases*
Cystic hygroma	3
Non-immune hydrops	2
Exomphalos	2
Spina bifida and hydrocephalus	1
Holoprocencephaly	1
Anencephaly	1
Double outlet right ventricle and hydrocephalus	1
Ventricular septal defect, cleft palate and microcephaly	1
In utero growth retardation	1

Table 2 Antenatal ultrasound abnormalities in liveborn babies

Abnormality	*No of cases*
Arachnoid cyst	2
Small exomphalos	2
Diaphragmatic hernia	1
Dilated renal pelvis	1
Double outlet right ventricle	1

weeks of gestation, because of polyhydramnios and severe intrauterine growth retardation. Ultrasound abnormalities detected in those who were not liveborn are shown in table 1. Of the 13 cases diagnosed by ultrasound, five were confirmed by amniocentesis and one was confirmed by chorionic villus biopsy.

Of 34 live born babies, only two had a firm antenatal diagnosis: one was diagnosed at 14 weeks but had a karyotypically (and subsequently clinically) normal twin; and one was the 34 week diagnosis already mentioned. Three parents declined amniocentesis, offered on the basis of maternal age. Of the remaining 29, all but three were noted to be growth restricted in utero on routine scans and seven had definite abnormalities (table 2).

CYTOGENETICS

Cytogenetic confirmation was made in 65 cases and clinically (JB) in one 33 week gestational age stillborn baby. Trisomy 18 was confirmed in 31 of the live babies with one translocation (child 47,XX + 18 t(11;18) (q13.1;q23), mother 46,XX t(11;18) (q13.1;q23), father 46,XY, one child with 48,XXX + 18, and one child with 47,XX + 18/46,XX mosaicism. The

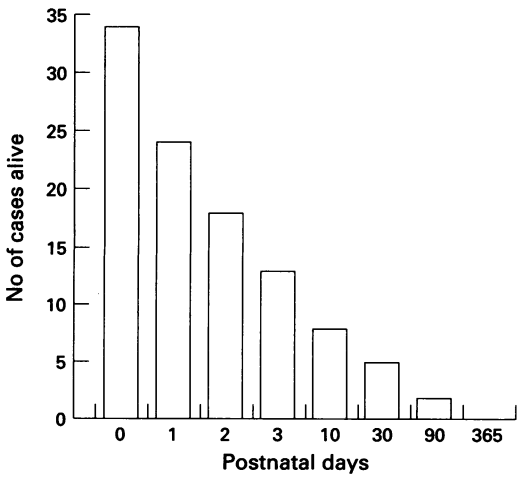

Figure 1 Postnatal survival of infants studied.

Table 3 Heart malformations in liveborn babies

Heart malformation	*No of cases*	*Median survival*
Hypoplastic left heart syndrome	3	2 days
Aortic coarctation	1	3 hours
Transposition of the great arteries + ventricular septal defect	1	5 hours
Ventricular septal defect	7	6 days
Complete atrio-ventricular septal defect	5	2 days
Double outlet right ventricle	2	2 days
Tetralogy of Fallot	1	1 hour
Subvälvar pulmonary stenosis	1	2 days

clinical features of these three children were similar to those of the other liveborn babies and they were included in the analysis.

MODE OF DELIVERY

Twenty one cases (64%) were delivered by caesarean section. In only one case was the diagnosis of trisomy 18 known beforehand, and this was the twin pregnancy where the safety of the normal fetus was compromised by presentation of the affected twin. Of the remainder, caesarean section was performed for fetal reasons in 13 cases (fetal distress (n=11), cord prolapse (n=2)). Obstetric indications for the others were breech position or transverse lie (n=4), previous section (n=1), poor prognosis and previous section n=(1) and intrauterine growth retardation (n=1).

SURVIVAL

The average gestation at birth of those born alive was 37 weeks, with a mean maternal age of 27.5 years and a mean birthweight of 1.8 kg. The median survival was 3 days with only nine babies living longer than a week and none longer than a year (fig 1).

Twenty five babies had either a postmortem examination (n=9), or an echocardiogram (n=13), or both (n=3). This confirmed congenital heart disease in 21 cases and a normal heart in four. Of the remaining nine liveborn babies, six had no clinical evidence of a murmur or cardiac failure, two had murmurs but no cardiac failure (and both died of apnoea), and there were insufficient data in one baby dying at 6 hours of age. The 21 with confirmed heart malformations are summarised in table 3. Only five had malformations which might have caused early death. Three babies had hypoplastic left heart syndrome and died within the first two days. One baby had coarctation, ventricular septal defect, and patent arterial duct, and died at 3 hours; and one baby had transposition of the great arteries and a ventricular septal defect and died at 5 hours.

MODE OF DEATH

Detailed analysis of medical and nursing notes revealed the mode of death in all but two

Table 4 Mode of death

Classification	*No of cases*	*Median survival*
Never stabilised	9	4 hours
Apnoea	10	5 days
Episodic cyanosis	4	3 days
Sepsis	3	5 months
Extubated	3	3 days
Unknown	2	28 days

babies who died at home. The deaths of the three babies with hypoplastic heart syndrome were attributed to their cardiac malformation. Table 4 shows the survival for the five classifications. There was no association between the cardiac malformations and the mode of death except for the two babies with double outlet right ventricle who both died with episodic cyanosis at 2 and 3 days of age, although these babies showed no sign of cardiac failure.

Discussion

The reported prevalence of trisomy 18 varies enormously and reflects the way in which data are collected.[1 2 10 11] The birth prevalence in this study is similar to that in recently published studies from Utah [3] and Denmark.[10] The relatively small numbers in each series may account for the differences, but earlier studies may have omitted babies dying before chromosomal analysis. We present the observed prevalence of 1 in 4272 at 18 weeks rather than an estimate.

Three children were included with translocation and mosaicism. The latter has been associated with long term survival,[13] although mosaicism may have a different phenotype, with longevity simply representing the range of the condition.[6] More females than males were born alive, although fetal numbers are equal. Females also survived longer, confirming the trend noted by Weber,[11] Carter,[2] and more recently by Root.[3]

In this study 43% of cases were detected antenatally. This may affect the spectrum of abnormalities among those born alive, as severely affected fetuses are more likely to be detected. The mean liveborn weight in this series was 1.8 kg at an average gestation of 37 weeks, confirming other reports.[1] Most cases had in utero growth retardation after routine antenatal assessment, and some had ultrasound abnormalities (table 2), although no further diagnostic action was taken. Schwanitz [12] has suggested that 20% of the cases of intrauterine growth retardation, and 40% of those with a heart defect, will have a chromosome disorder, with trisomy 21 and trisomy 18 being the most common. Other ultrasound abnormalities, such as hand posturing, have also been strongly associated with autosomal trisomies.[13] Most cases of intrauterine growth retardation were not detected until the late second or third trimester when the fetus would be potentially viable. However, the high incidence of delivery by caesarean section reported by David,[14] Young,[1] and confirmed in this series, might be reduced further by investigation of unexplained intrauterine growth retadation. Rapid karyotyping by funipuncture or placental biopsy has been recommended to facilitate management.[13] In the 13 cases where section was performed for fetal reasons alone (fetal distress and cord prolapse), prior confirmation of trisomy 13 may have helped clinicians and mothers to proceed with vaginal delivery.

Only three cardiac malformations were detected antenatally, and of these, only one baby was liveborn (table 2), despite the high prevalence of potentially detectable abnormalities (table 3).[15] It is not clear why so many cardiac abnormalities were missed, but equipment and training has recently improved throughout the region, and detection rates from scans showing obstetric anomaly are already improving.

Median survival was similar to that in other recent series[1 2 3 10] and no baby in this series lived longer than one year. Hecht's self fulfilling prophecy,[16] that active management is withdrawn after diagnosis, certainly affects early deaths but probably has less effect on subsequent deaths. More aggressive treatment in the first few days and subsequent intensive support may explain the increased occurrence of prolonged survival in the United States[6] but this may also be due to case ascertainment. Long term survival is well documented even in the absence of mosaicism, but not in population studies, and the relatively small numbers in this series may account for the lack of it.

The spectrum of congenital heart disease in this series is similar to that of previously reported postmortem [17] and echocardiographic series.[18] However, absence of transposition of the great arteries in trisomy 18 was reported by Van Praagh[17] as a strong if not absolute criterion for fetal echocardiographic diagnosis. We found no previous reports of transposition in cytogenetically confirmed cases. In this series a 36 week gestational age, live born male weighing 1.6 kg died at 5 hours of age. Postmortem examination confirmed the cardiac diagnosis of transposition with ventricular septal defect, and trisomy 18 was confirmed cytogenetically.

The recent paper by Baty *et al*[6] provides interesting information regarding trisomy 18, but ascertainment bias may produce a distorted natural history. Specifically it concentrates on survivors and is unable to provide information on the mode or cause of death other than cardiorespiratory arrest. In the present study detailed examination of medical, and more usefully, nursing notes, indicates central apnoea as the most common mode of death (10 cases). In only one case was this associated with cardiac failure which had been successfully treated. Only the babies with hypoplastic left heart syndrome may have died as a result of their cardiac malformations, and these died very young. In all, nine babies died within a few hours of birth and were either not resuscitated (n=2) or had further active management withdrawn in the face of overwhelming problems and a clinical diagnosis of trisomy 18. No baby living longer than 2 days died of demonstrable cardiac complications. Cardiac surgery would not, therefore, have affected their survival.

Clinicians have long recognised the poor outcome of trisomy 18. This study provides population based information to aid management and counselling. Many apparently potentially detectable cases are still missed antenatally. Their detection would increase parental choice not only of termination but also of delivery. The high incidence of caesarean birth

might be reduced. Despite popular belief, cardiac malformations are not often directly lethal. The most common mode of death is central apnoea as in trisomy 13.[19]

We are grateful to all the staff at the Fetal Abnormality Survey, in particular Mrs Marjorie Renwick, to Dr E Hey for his helpful comments, and to all those contributing information to the survey. We also thank Mrs Pauline Baker for typing the manuscript.

JPW was supported by the Sir Jules Thorne Charitable Trust.

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